COMMENTS ON THE *PROPOSAL FOR THE INCLUSION OF METHYLPHENIDATE ON THE WHO MODEL LIST OF ESSENTIAL MEDICINES FOR THE TREATMENT OF CHILDREN AND ADOLESCENTS AGED 6-17 YEARS WITH ATTENTION-DEFICIT/HYPERACTIVITY DISORDER*

We have some concerns regarding the consistency and completeness of the data reporting and summarization in the above referred proposal (1) which may impact its overall validity.

First, the application refers to the issues raised by the Expert Committee regarding the two previous applications for including methylphenidate for children aged 6 to 17 years on the Essential Medicines List (EML) and the Essential Medicines List for Children (EMLc). The Expert Committee highlighted the necessity for long-term evidence from randomized clinical trials (RCTs) with a minimum duration of 12 months. The current proposal claims to include findings from two RCTs, both exceeding 12 months in duration (2, 3), as well as a randomized discontinuation trial (4). We contend that the evidence presented does not provide robust support for the use of methylphenidate for durations exceeding 12 months. This discrepancy necessitates a critical reassessment of the reliability and applicability of the data.

The Multimodal Treatment Trial (MTA) trial (2) is often cited as a significant study in the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD), yet it presents notable methodological limitations. One critical issue is the absence of a placebo control group, which is essential for distinguishing genuine treatment effects from placebo responses, spontaneous remission, or regression to the mean. The Expert Committee has emphasized that trials lasting over 12 months should incorporate a placebo control group to enhance the validity of the results. Furthermore, the MTA trial involved children aged 7 to 9 years who were randomly assigned to four treatment regimens: a) medication alone, b) behavioral treatment alone, c) a combination of medication and behavioral treatment, or d) community treatment. After 14 months, the results indicated that both combined treatment and medication alone were superior in reducing symptoms compared with behavioral treatment alone and the control group. At all subsequent time points, medical treatment alone or in combination with behavioral treatment was not superior to the other groups (5). Also, the absence of a placebo control group raises significant concerns about the internal validity of these findings.The methodology of the MTA trial suffered from insufficient blinding of participants, personnel, and outcome assessors, which can introduce bias and increase the risk of type I errors, thereby lowering the certainty of the evidence (6). This lack of blinding is a critical limitation that has been noted in other studies as well, where the absence of blinding can lead to inflated placebo responses and skewed results (7).

The Barragán et al. trial is an unblinded trial with several limitations (3). It lacked a formal sample size calculation, resulting in a small sample, and did not include a placebo control arm (3).

The Matthijssen trial faced issues with incomplete data, as analyses were conducted on the full dataset, which included all participants who received at least one dose of the trial drug. For those who withdrew, the researchers used ratings obtained at the time of trial termination. Notably, the authors of the Matthijssen trial stated: “[...] the fact that most participants in our study did not experience significant worsening after discontinuation of methylphenidate supports guideline recommendations to periodically assess whether there is a continued need for methylphenidate

treatment [...]" (p. 760) (4). Further limitations of this study were that participants did not have a formal ADHD diagnosis, and the sample size was small, with only 120 participants.

Further, this third proposal for the inclusion of methylphenidate on the EML and EMLc for children and adolescents aged 6 to 17 years (1) cites the 2023 World Health Organisation Mental Health Gap Action Programme (WHO mhGAP) guideline for the treatment of Attention-Deficit/Hyperactivity Disorder (ADHD) (8). The guideline recommends that methylphenidate should be a treatment option "for those with ADHD in the context of a management plan that addresses psychosocial risks and vulnerabilities and environmental factors that have an impact on symptoms and functioning" ((8), p. 3, line 31). While the guideline does endorse methylphenidate, it is crucial to recognize that this recommendation is contingent upon a comprehensive approach to ADHD management. The application appears to overlook the guideline's emphasis on the evidence of low certainty.

The WHO mgGAP guideline for ADHD treatment also warrant scrutiny, as they are primarily based on a network meta-analysis by Cortese et al. that exhibit low-certainty evidence (9). This low certainty implies that the true magnitude of treatment effects remains unclear, which is a significant concern for clinical practice (10). The mgGAP guidelines highlight the necessity for specialist assessment prior to the prescription of methylphenidate, given the risks associated with its misuse. This is in clear contrast with the proposal for primary care providers to manage ADHD without specialist oversight and raises ethical and clinical concerns.

In summary, while the MTA trial has contributed to our understanding of ADHD treatment, its methodological limitations — particularly the lack of a placebo control group and blinding — significantly undermine the reliability of its findings. The Barragán et al. trial is an unblinded study without a placebo control arm, and the discontinuation trials also have several limitations (2, 3).. In our opinion, these data do not provide reliable or valid evidence regarding either the effectiveness or harms of long-term methylphenidate treatment. The WHO mgGAP guideline based on low-certainty evidence further complicate the clinical landscape for ADHD management. Future research must prioritize rigorous methods to ensure that the evidence base for ADHD treatment is both robust and reliable.

The proposal advocates for a more integrated approach to diagnosing and treating children and adolescents with ADHD within primary care settings. Expanding the authority to prescribe medication in the primary sector could lead to a higher prevalence of ADHD diagnoses and medical treatment. This perspective also raises significant concerns, particularly in light of the alarming trend observed in Eastern Finland, where 20% to 25% of children are receiving medical treatment for ADHD (11). Such a high prevalence of pharmacological intervention may indicate an over-reliance on medication without adequate consideration of alternative management strategies, potentially leading to unrealistic expectations regarding treatment outcomes.

Regarding prevalence, it is important to note that while the authors of the proposal claim that the diagnosis is reliable based on field trials, real-world data from Norway—despite its comprehensive and universally accessible mental health care system—reveals significant variability in the symptom threshold required for an ADHD diagnosis. This suggests that the real-world reliability of the diagnosis is, in fact, very low (12) Furthermore, while the authors note persistence rates of ADHD

into adulthood of around 50%, there is substantial variance in prevalence estimates regarding adult ADHD with the long-term birth cohort studies showing the lowest estimates by a large margin (≈0.5 to ≈1.0% is cohort studies and 2.58% in a review across methodologies) (13-15).

Noteworthy, we do *not* believe that extending ADHD management to primary care will benefit the field, as the risk of overdiagnosis and overtreatment is high (16). The applicants refer to the mhGAP guidelines, which clearly outline the necessary prerequisites before initiating pharmacological treatment: "Children and adolescents receiving methylphenidate should be maintained under close clinical monitoring for symptom improvement and the prevention of adverse effects. A specialist care provider trained in ADHD management should reassess the child or adolescent's treatment plan at least once per year. The rationale for specialist assessment before prescribing methylphenidate is that diagnosing ADHD requires specialist clinical judgment, particularly given the risks of methylphenidate misuse."

Finally, we would like to address the misunderstanding exhibited by the authors of the proposal regarding our systematic review published in the Cochrane Library in 2023 (17). Following their reassessment, they state that the main evidence from this review ought to be rated at moderate certainty for both benefits and harms, contrary to our original assessment of low or very low certainty. We disagree with this interpretation, as it misrepresents the findings and undermines the rigor of our systematic review process, which was conducted following strict methodological guidelines from the Cochrane Handbook (10) and the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) recommendations for rating certainty of evidence(18).

It is crucial to maintain fidelity to the evidence as presented in our review, which underscores the need for cautious interpretation of the data. The authors of the proposal are discussing the GRADE assessment in our Cochrane systematic review on the benefits and harms of methylphenidate for children and adolescents with ADHD (17). The authors argue that we have been overly strict in rating the evidence as low certainty or very low certainty. In particular, the proposal authors disagree with our decision to downgrade the evidence due to the risk of bias by two points and our assessment of heterogeneity. The reason that we downgraded the evidence by two points for risk of bias is that each trial outcome was often judged as unclear or high risk of bias on multiple bias risk domains, often including the high likelihood of unblinding due to easily recognizable adverse events. This concern is, in fact, acknowledged by the European ADHD guideline group (19). The applicant points out that there is divergent evidence on the impact of blinding in meta-epidemiological studies, citing Moustgaard et al., who concluded that blinding did not significantly affect effect estimates, a finding supported by many other researchers (20).

However, the results of the Moustgaard et al. study contradicts previous findings from a larger meta-epidemiological study by Savovic et al (6), in which the authors found that "intervention effect estimates were, on average, exaggerated in trials with high or unclear (versus low) risk-of-bias judgements for sequence generation (ratio of odds ratios (ROR) = 0.91, 95% credible interval (CrI): 0.86, 0.98), allocation concealment (ROR = 0.92, 95% CrI: 0.86, 0.98), and blinding (ROR = 0.87, 95% CrI: 0.80, 0.93)". These results led the authors to conclude that "Inadequate randomization and lack of blinding may lead to exaggeration of intervention effect estimates in randomized trials". Hence, due to the new and contradicting findings from the Moustgaard et al. study, the authors concluded

that: *At this stage, replication of this study is suggested, and blinding should remain a methodological safeguard in trials." (20)*. Meta-epidemiological studies conclude that randomized trials at no or unclear blinding are associated with biased overestimation of intervention effects (21).

The authors' claim that we should not have downgraded the evidence for heterogeneity suggests that they are not as familiar with the data in our review as we are. While we did downgrade for heterogeneity — perhaps more than the authors deem appropriate — this decision must be viewed in the context of the factors for which we did not downgrade. For instance, we did not downgrade for indirectness, despite significant variations in rating scales used to assess the primary outcome of ADHD symptom severity. Additionally, we did not downgrade for indirectness related to differences in ADHD diagnoses, even though we pooled different ADHD subtypes (17).

In conclusion, the lack of high-quality, long-term placebo-controlled trials still raises concerns about both efficacy and safety. Given the significant methodological limitations and misinterpretation of key evidence, we remain unconvinced that this proposal provides a robust basis for including methylphenidate on the EML and EMLc. This is the third proposal advocating for the inclusion of methylphenidate for children and adolescents with ADHD. The first two were rejected by the WHO (22, 23), and we do not believe this third proposal presents any new evidence that would alter the decision. Future research should prioritize long-term, placebo-controlled trials to strengthen the evidence base. Until such evidence becomes available, the inclusion of methylphenidate on the EML and EMLc should be carefully considered in light of the unresolved uncertainties regarding its long-term safety and effectiveness.

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